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Animal Stereotypy

5 The present invention relates to the treatment, prevention or amelioration of animal stereotypies.

10 Stereotypies are animal behavioural disorders. They are characterised by the performance of repetitive, invariant movements which have no obvious function. Equine stereotypies are of particular concern to owners of horses because the condition and performance of a horse which displays stereotypic behaviour is often adversely affected. This can substantially reduce the market value of a horse. Equine stereotypies include oral stereotypies such as crib-biting, wood chewing and wind-sucking, and locomotor stereotypies such as weaving and box-walking.

15 The cause or causes of stereotypies are not known. This lack of knowledge has severely hampered the development of effective treatments and preventatives for stereotypies. In the abstract of a study by Christine Nicol and Amanda Waters, entitled "The treatment and Prevention of Equine Stereotypies", theories on possible causes of equine stereotypy are given. It is noted that stereotypies are frequently regarded as functionless pathologies of the nervous system. It has also been proposed that oral stereotypies serve some digestive function. Alternative views are that they are developed by an animal as a way of dealing with stress or boredom. A further theory is that animals learn to perform stereotypies by imitating other animals that perform them.

25 Preventative measures for equine stereotypy based on these theories include use of stable toys to stop a horse from becoming bored or stressed, or isolation of a horse from other horses to stop it from learning stereotypies by imitation. Treatment of oral stereotypies such as crib-biting can involve more harsh measures, for example fitting

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the horse with a collar to prevent it from crib-biting, or even surgery. Typically, surgery involves cutting the ventral neck muscles and/or the nerves that supply them. Other forms of control include aversion therapy. Here, the horse may be given an electric shock, or physical admonishment when it performs a stereotypy.

The above treatments or preventative measures have been found to be unsatisfactory. Use of stable toys has not been found to be an effective way of preventing equine stereotypy. Physical prevention of stereotypy, either by use of a collar or surgery, is not successful because the animal still has the urge to perform the behaviour. When the collar is removed, a horse will often perform a stereotypy more intensively than before. After surgery, the animal may still be able to perform the stereotypy by utilising other muscle groups. Preventatives such as social isolation, collar fitting, aversion therapy and surgery are undesirable.

In the abstract by Nicol and Waters referred to above, it is disclosed that an epidemiological study has shown that a significant number of horses develop stereotypic behaviour during the immediate post-weaning period. At weaning, the mare-foal bond is broken, but feeding and housing practices are often also changed at this time. The discovery that stereotypic behaviour often begins in the immediate post-weaning period has not so far led to a treatment or preventative for stereotypy because it is not clear which factor or combination of factors are significant in the onset of stereotypy.

Some studies have reported a link between behavioural abnormalities and acidity in the hindgut. Johnson et al (Equine Veterinary Journal 1998, 30(2), 139-43) noted a reduction in abnormal behaviour when horses were administered Founderguard (containing 1% virginiamycin). The most obvious explanation for this is stated to be reduced

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acidosis in the hindgut caused by suppression by virginiamycin of lactic acid production in the hindgut.

Willard et al (Journal of Animal Science 1977, 54(1), 87-92) discloses that horses fed a concentrate diet with hourly infusions of sodium carbonate were observed to spend less time chewing wood and performing coprophagy (eating faeces) than horses fed a concentrate diet alone. The infusions of sodium carbonate significantly increased caecal pH. It was concluded that increased caecal acidity may influence the horse's desire to practice coprophagy and wood chewing.

The link between acidity in the hind gut and abnormal behaviour is also reported in WO 96/20709. This document discloses that starch, sugar or other carbohydrate which enters the hind gut is rapidly fermented to form lactic acid. This accumulation of lactic acid is stated to lead to a decline in hindgut pH which results in a wide range of biological consequences, including behavioural abnormalities. Methods of treatment or prophylaxis of adverse behaviour are disclosed in which an effective amount of an agent capable of preventing or controlling fermentative acidosis in the hindgut is administered to an animal.

Agents disclosed in WO 96/20709 as being capable of preventing or controlling fermentative acidosis are: antibiotic type compounds such as Virginiamycin (stated to be active against bacteria which produce lactic acid); enzymes which increase the digestion of carbohydrate and decrease the amount of rapidly fermentable carbohydrate passed to the hindgut; and clay preparations which bind specific ions to reduce the adverse effects of rapid fermentation of starch and other soluble carbohydrates in the gastrointestinal tract.

However, there are disadvantages to use of these agents. Virginiamycin is believed to have growth promoting activity. Consequently, this side effect may make

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manufacture of a medicament for the treatment, prevention, or amelioration of animal stereotypy.

There is also provided according to the invention use of a stomach antacid in the manufacture of a medicament for the treatment, prevention, or amelioration of animal stereotypy.

There is also provided according to the invention a method of treatment, prevention, or amelioration of animal stereotypy which comprises controlling the stomach pH of an animal.

The stomach pH of the animal may be controlled by administering a composition according to the invention to the animal.

There is also provided according to the invention a method of treatment, prevention, or amelioration of animal stereotypy which comprises preventing or reducing ulcer formation in the stomach of an animal or treating ulcers formed in the stomach of an animal. Ulcer formation may be prevented or reduced, and ulcers may be treated, by administering a composition according to the invention to the animal.

The amount of fat in compositions according to the invention is preferably from about 5% to about 20%, more preferably from about 8% to about 17%, by weight of the composition. Preferred fats are highly polyunsaturated vegetable oils. These fats tend to be highly palatable and easily mixed into other components of compositions of the invention. Examples are corn oil, soya oil, or processed canola oil. Other preferred fats are more saturated fats which are more stable and, therefore, are less prone to rancidity. Examples are coconut oil, palm oil, or sunflower oil.

"Fibre" as used herein means carbohydrate which is not digestible by mammalian enzymes. Some of the fibre may be fermentable by microbial enzymes. The amount of fibre in compositions according to the invention should be sufficient

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to extend the amount of time spent chewing the composition by an animal administered with such a composition. The amount of fibre in a composition of the invention may be measured as the amount of crude fibre or neutral detergent fibre (NDF). The amount of crude fibre in compositions according to the invention is preferably from about 3.5% to about 35%, more preferably from about 10% to about 25%, by weight of the composition. The percentage of crude fibre in a sample is the percentage of the matter remaining in the sample after treatment with acid and alkali. This is measured by treating the defatted sample successively with boiling solutions of sulphuric acid and sodium hydroxide. The residue is filtered, washed, weighed and ashed. The loss of weight on ashing corresponds to the weight of fibre present in the test sample. The amount of NDF in compositions according to the invention is preferably from about 15% to about 70%, more preferably from about 25% to about 50%, by weight of the composition. This can be calculated using a method such as that described in Agric. Handbook No.379 (1970) Goering H.H. and Van Soest P.T. (USDA Washington D.C.).

Preferably at least some of the fibre is chopped fibre. Preferably the chopped fibre is about 1-7cm long. Preferably at least some of the fibre also has a high protein concentration. A preferred example is alfalfa hay.

The starch content of compositions according to the invention is preferably low, suitably below about 20% by weight of the composition. Feed stuffs which comprise high amounts of fat and fibre and low amounts of starch are especially preferred as components of compositions of the invention. An example is rice bran.

Suitable stomach antacids for use in compositions and methods of the invention may act by neutralising stomach acid or by inhibiting secretion of acid into the stomach. Any alkali which neutralises stomach acid and can be safely administered to an animal may be used. Suitable antacids

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which act by neutralising stomach acid include Neigh-Lox and prostaglandin analogues. The active ingredients in Neigh-Lox are dihydro-aluminium sodium carbonate and aluminium phosphate. Suitable antacids which inhibit acid secretion in the stomach include proton pump inhibitors and histamine type-2 antagonists which block histamine-stimulated gastric acid secretion. Substituted benzimidazoles, such as omeprazole, act as proton pump inhibitors. Cimetidine and ranitidine are examples of Histamine type-2 antagonists.

It is believed that once an animal has learnt a stereotypy, the stereotypic behaviour becomes fixed and the animal will perform the stereotypy even if the original cause of the behaviour has been removed. Consequently, the animal should be treated using a composition or method according to the invention before any stereotypic behaviour becomes fixed, and preferably before, or soon after, the animal develops any stereotypic behaviour.

Acidity in the stomach is thought to increase when animals are fed meals of grain or are subjected to extended periods of fasting. Stomach pH may also decrease when the diet of an animal changes during weaning. Consequently, an animal should be treated with a composition or method according to the invention shortly before and/or during and/or following eating a high grain diet, undergoing a period of extended fasting, or weaning. Treatment at these times may be particularly effective in preventing, treating, or ameliorating animal stereotypy.

In order to minimise the risk of an animal developing a stereotypy, the animal may be treated with a composition or method according to the invention from birth.

Compositions and methods of the invention may also be effective when the animal being treated is a weaned animal.

It is considered that compositions according to the invention will usually be included with the diet of an animal being treated according to the invention.

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Compositions according to the invention may be included in the diet of the animal's mother while she is lactating. This is because the mother's diet influences the nutritional content of the milk which the animal receives and because the animal may eat its mother's feed before it is weaned; foals invariably eat their dam's feed before they are weaned.

Compositions according to the invention may be included in feed and the said feed fed to the animal as it is being weaned onto solid food.

Compositions according to the invention may be included in the animal's diet post weaning.

The invention is further described by the following embodiment. The embodiment relates to use of stomach antacid to treat, ameliorate, or prevent crib biting in horses.

Example

Methods

Advertisements were placed for foals to take part in the study. Foals offered for the study were rejected if the foal had been crib-biting for more than 20 weeks, was more than 1 year of age, or if the owner had attempted to prevent crib-biting using surgery or electric shock treatments.

Foals chosen for the study were visited at times when the owners had previously noted crib-biting behaviour. They were observed for a minimum of 1 hour to establish that they were performing crib-biting behaviour. It was clear from the observations that some owners had mistaken wood-chewing for crib-biting.

A crib-biting horse grasps a fixed object with its incisor teeth, arches its neck, and pulls back (often but not always

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emitting a grunting sound). There is no ingestion of wood, or other substrate. The behaviour is invariant in form - it tends to occur in the same place, or perhaps 2 or 3 favoured sites, within the stable, at the same time in a sequence of behaviour (for example a horse may grasp a piece of hay, move to the front of its stable, then crib-bite), and at the same times of day (for example just after feeding). The crucial part of crib-biting is arching of the neck which puts considerable tension on the neck muscles, and affects the oesophagus and pharynx.

Wood chewing is completely different and cannot be distinguished in form from normal chewing at hay, straw or bark. Wood or other material is ingested and chewed. The wood or material may or may not be swallowed. The horse is not tense during this behaviour. A horse will perform wood-chewing in a variety of places (wherever a new bit of wood can be found), and does not perform the behaviour as part of a fixed sequence of behaviour.

Those foals observed to be wood-chewing were rejected from further study. The remaining foals were randomly allocated to a feed treatment, and their owners were provided with an initial supply of the diet for that treatment and asked to gradually change their foals onto this diet over the subsequent week.

In total, 13 crib-biting foals and 8 control foals (belonging to 13 different owners) were recruited. Comparisons were made between the two populations and are summarised in Table 1.

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Table 1 General Characteristics of Study Population

	Crib-biting foals		Normal foals	
	mean	se	mean	se
Age at entry (days)+	233.7	9.21	291.2	47.45
Age at weaning (days)	172.38	9.00	183.62	15.20
Age when concentrate introduced (days)	40.0	18.1	51.2	29.80
Amount of concentrate fed prior to entry (kg)	2.64	0.30	2.61	0.40

+ Entry into the study was taken as the first date on which detailed behaviour observations were taken

Crib-biting foals had developed crib-biting behaviour at an average of 152.5 (se 20.3) days of age, or 21.8 weeks. A proportion of the foals had developed oral stereotypy prior to weaning. They had been performing stereotypic behaviour for a mean 88.7 (se 13.3) days, or 12.7 weeks, prior to entry into the study.

Treatments

Six crib-biting and four control foals were allocated to a typical base diet containing cereals (wheat, barley, oats), wheatfeed, soya bean meal, peas, full fat linseed, vitamin and mineral supplements, and molasses. This base diet was supplemented with forage (fresh or preserved). This is Diet A. This diet was re-bagged before delivery to the owners and was fed according to body weight.

Seven crib-biting and three control foals were allocated to an antacid diet. This was Diet A, re-bagged and supplied with a tub of Neigh-Lox. Owners were asked to feed

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approximately 125g of Neigh-Lox per day, divided equally among feeds.

5 One control foal for which initial samples and endoscopy results were obtained was not placed on a diet as its crib-biting partner moved to a different yard.

Behavioural Observations

10 Participants were visited regularly throughout the trial. Owners were asked to ensure that their foal was in an environment where it had been observed crib-biting for at least one hour before the behaviour recordings were started. The time of day, and time in relation to meal-time, that
15 observations were taken varied among foals, but was generally held constant for each foal in the study across repeated visits.

Endoscopy

20 Foals were endoscoped during the first week of the trial, and a week after the trial had ended. All foals were deprived of all feed and forage for a period of 12 hours overnight and endoscoped between 0900 and 1030 hours the
25 next morning. During endoscopy. A continuous video record was made of the glandular and squamous mucosa. Samples of gastric fluid were taken and the pH measured. The veterinarian performing the endoscopy then provided a written description of his observations. An independent
30 observer who was not given information about which horses were crib-biters, or about which feed treatment they had received also prepared a descriptive account from the video recordings. This was compared and the written description prepared at the time by the veterinarian. The information
35 was summarised according to an agreed scoring system.

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RESULTS

Baseline correlations among variables and differences between crib-biting and normal foals at the start of the trial.

(i) General Characteristics

None of the normal foals started to crib-bite during the trial.

There were no significant differences between crib-biting and normal foals in any of the general population parameters, although despite very small numbers, there was a trend towards an association between crib-biting and previous administration of antibiotics.

(ii) Endoscopy

Endoscopy records were obtained for 10 crib-biting and 4 control horses at the start of the trial.

Ulcers were observed in 6 foals at the start of the trial. The ulcers were few in number and generally mild, with the exception of 1 crib-biting foal that had extensive ulceration. The crib-biting foals had higher scores for number of bots, severity of ulcers and inflammation than the normal foals at the start of the trial, and lower scores for stickiness of the mucosa, black flecks on the mucosa, corrugations of the squamous mucosa and folding of the glandular mucosa. The squamous mucosa and glandular mucosa were also less moist in crib-biting than normal foals.

The mean pH of the gastric fluid samples taken from 5 crib-biting foals on the first endoscopy visit was 1.69 with a range between 1.43 and 2.00.

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Treatment Effects**(i) Behaviour**

The data on frequency and duration of crib-biting is shown in Tables 2 and 3. It should be noted that the management of some of the foals changed during the course of the study. These foals were No. 1: in all the time (observations 1 and 2) to out all the time (observation 3); No. 3: in at night or in all of the time if wet (observations 1 and 2) to out all of the time (observation 3); and No. 13: hay fed as forage (observations 1 and 2) to haylage fed as forage (observation 3). The third observation period for these 3 foals was therefore not used in analysis.

Table 2 The frequency of crib-biting (mean bites per hour) exhibited during the trial

Foal	Diet	Obs period 1	Obs period 2	Obs period 3
1	Control	187.3	85.5	(3.8)
2	Control	5.5	0.0	0.0
3	Control	220.0	449.0	(225.0)
4	Control	48.4	2.5	0
5	Control	11.5	0.5	3.25
6	Control	62.7	70.0	73.5
7	Neighlox	4.5	0.5	0.0
8	Neighlox	60.5	478.5	155
9	Neighlox	285.3	204.9	223
10	Neighlox	111.5	47.7	Deceased.
11	Neighlox	30.0	16.3	9.00
12	Neighlox	13.5	20.5	13.9
13	Neighlox	41.25	16.75	(100)

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Table 3 - The duration of crib-biting (mean seconds per hour) exhibited during trial

Foal	Diet	Obs period 1	Obs period 2	Obs period 3
1	Control	894.5	821.5	(22)
2	Control	41.5	0.0	0.0
3	Control	976.0	2326.0	(691.0)
4	Control	278	23.3	0
5	Control	148	8.3	18.0
6	Control	599.7	574.5	674
7	Neighlox	89.2	5.0	0.0
8	Neighlox	364.8	2328.5	1007.0
9	Neighlox	1767.0	945	1278
10	Neighlox	455.5	172.2	Deceased

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The change in crib-biting frequency and duration was assessed by taking the slope of the values over the 3 month period. Four of the 13 crib-biting foals had positive slope values for both frequency and duration, indicating an overall increase in crib-biting behaviour during the trial. The remaining slopes were all negative.

Each foal was then ranked according to its change in behaviour over time, relative to the other foals in the study. The two measures of frequency and duration resulted in slightly different rank orderings of the foals. For both measures rank order 1 indicates the foal that showed the largest decline in crib-biting, and rank order 13 indicates the foal that showed the largest increase in crib-biting. The rankings are shown in Table 4 and were used to examine associations between stomach condition and behavioural change.

Table 4 Rank ordering of foals according to change in crib-biting behaviour during trial

Foal	Rank Order for frequency	Rank order for duration
1	1	5
2	8	9
3	13	13
4	5	3
5	7	6
6	11	11
7	9	7
8	12	12
9	3	2
10	2	1
11	6	4

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5 The relationship between ulcers and crib-biting behaviour was examined by comparing the extent to which crib-biting changed over the course of the trial, with the severity of ulcers present at the end of the trial. Horses whose ulcers did not heal during the course of the trial were also the horses that showed little or no reduction in crib-biting behaviour.

10 The results presented here demonstrate for the first time a relationship between stomach condition and abnormal oral behaviour in the horse and are consistent with crib-biting being an adaptive attempt to reduce stomach acidity. Crib-biting foals tended to have more bots and ulcers, a drier and more expanded stomach wall, and a greater degree of
15 inflammation than normal foals. The general appearance of the stomach of the crib-biting foals supports the hypothesis that their stomachs are more acid. The results also show that an improvement in stomach condition was associated with reduced crib-biting behaviour. Administration of Neigh-Lox
20 was associated with a resolution of mild ulceration. Foals whose mild ulceration cleared showed the greatest improvement in crib-biting. In some of these foals crib-biting ceased altogether.

25 The cause of the stomach problems in crib-biting foals is not clear. Candidate factors include:

- The early introduction of concentrate feed.

30 Most of the crib-biting foals in the study had received concentrate feed from birth, or during the pre-weaning period. It is known from other work that concentrate feed increases gastric acidity, and causes ulceration.

- Previous illness or use of antibiotics.

35 The owners of some foals reported that they had started crib-biting during a period of illness or after receiving antibiotics. Illness may involve confinement and separation and foals may not feed properly during such periods.

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Alternatively, antibiotics may have a more direct effect in disrupting the flora of the hindgut.

- Sustained effects originating at weaning.

5 Weaning by methods that are particularly stressful increases the rate of development of stereotypies dramatically. Stressed foals are unlikely to eat, and feed deprivation is known to increase gastric acidity.

- Differential production of saliva.

10 It is possible that there is variation among foals in the extent to which they release saliva, either spontaneously or during feeding. The production of a limited supply of saliva may cause or enhance stomach acidity. The foals that do the most crib-biting may be the ones that most need to produce saliva and are most frustrated by their inability to
15 do so in sufficient quantities.

20 The data presented in the example demonstrate the effectiveness of a stomach antacid on the prevention, treatment, or amelioration of equine crib-biting. This activity is thought to be enhanced by the inclusion in compositions according to the invention of fat and fibre.

25 Compositions and methods according to the invention may be particularly effective at preventing stereotypy when the animal being treated is a weaning or recently weaned animal. Foals are typically weaned when they are four to six months old.

30 Use of compositions and methods according to the invention may be particularly effective in the amelioration, treatment or prevention of any stereotypy in all *equidae*, non-ruminant herbivores, and non-ruminant omnivores, for example crib-biting, wind-sucking, weaving and box-walking in equine animals.

35 Use of compositions and methods according to the invention may be particularly effective in the amelioration, treatment or prevention of stereotypies linked with gut function in all *equidae*, non-ruminant herbivores, and non-

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ruminant omnivores, but especially in the amelioration, treatment or prevention of equine crib-biting.

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5 The reason that compositions and methods according to the invention may be particularly effective in the amelioration, treatment or prevention of animal stereotypy is not known. However, the realisation that low stomach pH is linked with stereotypic behaviour suggests that pain caused by low stomach pH may cause the animal to perform a stereotypy, such as crib-biting, to stimulate the flow of

10 saliva into the stomach. This saliva would be expected to increase the stomach pH and alleviate the pain. The fact that significant numbers of horses develop stereotypic behaviour during the immediate post-weaning period may be because the diet of a foal changes significantly during weaning. If such a dietary change results in a persistent decrease in stomach pH, then stereotypic behaviour may be

15 more likely to occur. Administration of compositions according to the invention to an animal, especially a weaning or recently weaned animal, may ensure that its stomach pH is not persistently low and remove, therefore, the need for the animal to stimulate the flow of saliva into the stomach. It is believed that the fibre may help to prolong the time spent chewing by an animal. This in turn prolongs the production of saliva which neutralises stomach

20 acid. The fat is thought to delay emptying of the stomach so that the beneficial effect of the antacid and/or fibre is prolonged.

25 Compositions according to the invention may act by preventing or reducing stomach ulcer formation caused by prolonged periods of low stomach pH, or by treating stomach ulcers already formed.

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35 Compositions and methods according to the invention may be significantly more effective in the treatment and prevention of animal stereotypy than prior treatments and preventatives. In addition, treatment of animals using compositions and methods according to the invention does not

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involve any undesirable practices being performed on the animal.

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